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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,223	12/15/2004	Ning Man Cheng	090923-0103	7018

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,223	CHENG ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 47-56 are currently pending.

In response to a previous Office action, a non-final action (mailed on August 28, 2009), Applicants filed a response on November 19, 2009, is acknowledged.

Claims 47-56 are under consideration.

Applicants' arguments filed on November 19, 2009, have been fully considered but are not deemed persuasive to overcome the rejections as previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The previous rejection of claims 47-56 under 35 U.S.C. 103 (a) as being obvious over Vockley et al. (Arginase II, US 6316,199 B1, issue date 11/13/2001, see IDS) and Clark et al. (WO 02/44360, publication 6/6/2002, see IDS) in view of Mehvar et al. (Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation, J Pharm Pharmaceut Sci, 3(1):125-136, 2000, see PTO-892) and Takaku et al.(In vivo anti-tumor activity of arginine deiminase purified from Mycoplasma arginini, Int J Cancer. 1992 May 8;51(2):244-9, see IDS) is maintained. This rejection has been discussed at length in the previous office action and the rejection is maintained for the following reasons.

Instant claims are directed to a method of treating human liver, breast, colon or rectal malignancies comprising administering to a subject a modified, full-length recombinant human arginase I polypeptide of SEQ ID NO: 9 (without His-tag) encoded by SEQ ID NO: 8 or SEQ ID NO: 3 (with His-tag for claims 49, 50 and 53-55) encoded by SEQ ID NO: 2, which is covalently linked to polyethylene glycol (PEG), wherein administration of modified full-length recombinant arginase I polypeptide reduces physiological arginine level in the subject to below 10 μM for at least 3 days.

Vockley et al. teach human arginase II and I, wherein said arginase I is 100% identical to arginase I of SEQ ID BNO: 9 of the instant application, which degrades arginine to ornithine and urea, resulting in reducing the arginine level, and a method for treating human cancer including prostate cancer by administering arginase II

polypeptide (see Col 3, line 37-38). Vockley et al. also teach recombinant expression of human arginase II, expression in Sf9, Cos and *E. coli* followed by purification by affinity chromatography due to the presence of HA tag (Example 3 and 4), which results substantially purified protein (see Col 11, line 55-66). Vockley et al. further teach a pharmaceutical composition comprising human arginase II for treating said cancer (see Col 3, line 13-17) and pegylated said protein by treating with polyethylene glycol (PEG) to increase the half-life of the protein in serum and reduce the antigenicity to be an effective therapeutic composition for treating cancer (see Col 14, line 47-64). The arginase II gene was found using probes based on arginase I which was shown to have considerable sequence homology, wherein said arginase I is 100% identical to SEQ ID NO: 9 of the instant application. Vockley et al. does not disclose the composition comprises arginase I or the use of arginase I for treating liver, breast, colon, and rectal malignancies. Vockley et al. do not teach reducing arginine level below 10μM for at least 3 days.

Clark et al. teach modified arginine deiminase, an arginine degrading enzyme, which is modified with polyethylene glycol (PEG) and a method of treating cancer including sarcomas, hepatomas (a liver cancer) and melanomas (page 2, line 28-31, page 3, line 1-3). Clark et al. do not teach reducing arginine level below 10 μM for at least 3 days.

Mehvar et al. teach the half-life of arginase protein of 12 hrs after pegylation with polyethylene glycol and further teach that said arginase conjugate increased the

survival time in mice with Taper liver tumor (page 128, left column, line 3-8). Mehvar et al. do not teach reducing arginine level in the subject below 10 uM for at least 3 days.

Takaku et al. teach in vivo anti-tumor activity of arginine deiminase, an arginine degrading enzyme, in mice, wherein survival rate of the tumour implanted mice is substantially increased in arginine degrading enzyme injected mice (abstract, Fig. 7). Takaku et al. further teach the half life of arginine degrading enzyme is 4h in the blood of mice, and reducing the arginine concentration in the plasma of mice from 177 uM to 5 uM for 3 days after injecting said enzyme in the mice (Table I).

Vockley et al. indeed teach arginase I and a method of treating cancer with arginase II, an isoform of arginase I having identical function of degrading arginine, wherein said arginase II is modified with PEG, which increased the half life of arginase, which can be used for treating cancer including prostate cancer. Vockley et al. also teach HA-tagged arginase II. Clark et al. teach using arginine degrading enzyme for treating hepatomas, a liver cancer. Mehvar et al. teach treating mice with arginase protein (without specifying if it is arginase I or arginase II) modified with PEG, which increased the half-life of the pegylated arginase in mice to 12 hrs in a treatment of Taper liver tumor. Takaku et al. teach an in vivo anti-tumor activity of arginine degrading enzyme in mice, wherein said arginine degrading enzyme could reduce the arginine concentration in the plasma of said mice from 177 uM to 5 uM for 3 days

Therefore, combining the teachings of Vockley et al. Clark et al. Mehvar et al. and Takaku et al. it would have been obvious to one of ordinary skill in the art at the time of the invention was made to replace arginase II with arginase I as taught by

Vockley et al. and use the method of Vockley et al. to make a therapeutic composition comprising human arginase I pegylated with PEG as taught by Vockley et al. Clark et al. and Mehvar et al. for treating cancer including liver cancer as taught by Clark et al. and administering said pegylated arginase in a subject and reducing the arginine level around 5 uM for 3 days as taught by Takaku et al. and Takaku et al. clearly indicated that administered arginine degrading enzyme in a subject could reduce the arginine level around 5 uM for 3 days. The substitution of arginase II by arginase I is obvious because the two enzymes have identical activity and substituting HA-tag with His-tag is also obvious because of identical function for protein purification, which is well known and widely used in the art (claims 49, 50, and 53-55). See KSR Int'l Co. V. Teleflex, Inc. 82 USPQ2d 1385 (2007).

One of ordinary skill in the art would have been motivated to replace arginase II by "recombinant" human arginase I in view of its identical activity to arginase II, which has been shown to use in treating cancer by reducing the arginine level because cancer cell requires arginine for its proliferation and reducing said arginine eliminate cancer cells. One of ordinary skill in the art would have been motivated also to use pegylated arginase to increase the half-life of the enzyme, which will eventually reduce the serum arginine level below 10 uM (normal concentration is about 100 uM) for at least 3 days in serum to increase the effectiveness of the enzyme against malignant cell in order to treat cancer, since, reduced arginine helps cancer cell to die. Vockley et al. and Mehvar et al. clearly teach the increased half life of arginase protein by pegylation, which is effective for the treatment and one ordinary skill in the art would be able to increase the

half life of pegylated arginase I and subsequently decrease the arginine level below 10 uM for 3 days from the teachings of Takaku et al..

One of ordinary skill in the art would have a reasonable expectation of success because Vockley et al. could successfully used arginase II, which is an isoform of arginase I having identical function, i.e. arginine degrading activity for treating cancer.

Therefore, claims 47-56 would have been *prima facie* obvious to one of ordinary skill in the art.

Arguments/Response:

Applicants argue that the teachings of Vockley have been misinterpreted because Vockley does not teach a pharmaceutical composition for treating cancer and further argue that Vockley does not teach a method of treating cancer using Arginase II, but rather, Vockley teaches using Arginase II polypeptides "to treat diseases associated with or caused by as a defect in the Arginase II gene or Arginase II gene expression, such as, for example prostate disease, particularly prostate cancer." (col. 2, lines 35-46). Vockley lacks any teaching or suggestion of using Arginase II to treat cancer generally.

This is not found persuasive because in a 103 obviousness rejection, if the combination of prior arts teaches or suggests the claimed invention with proper motivation and expectation of success, then, each of the references does not need to teach or suggest each and every element of the claimed invention, which is proper. Vockley et al. indeed teach human arginase II and I, wherein said arginase I is 100%

identical to arginase I of SEQ ID BNO: 9 of the instant application, and a method for treating various diseases including human prostate disease in particular prostate cancer (see, Col 2, paragraph 6, lines 36-47). Vockley et al. also teach a composition comprising said arginase II polypeptide (see, Col 3, paragraph 3, line 13-17). The Examiner agrees that Vockley et al. also teach method of treating diseases associated with or caused by a defect in the Arginase II gene or Arginase II gene expression.

Applicants' also argue that Vockley does not indicate that human liver, breast, colon, or rectal malignancies are associated with or caused by a defect in the Arginase II gene or Arginase II gene expression. Thus, Vockley lacks any teaching or suggestion of using Arginase II let alone Arginase I for the treatment of human liver, breast, colon, or rectal malignancies.

This is not found persuasive because Vockley et al. do not need to teach or suggest of treating human liver, breast, colon, or rectal malignancies, but indeed teach or suggest that arginase II can be used for treating prostate cancer and thus, an ordinary skilled in the art would be motivated to test whether arginase II can be used for treating other malignancies including human liver, breast, colon, or rectal malignancies, which is obvious.

Applicants' further argue that Vockley fails to teach or suggest all elements of the independent claims, and this deficiency is not cured by any of the secondary references, a *prima facie* case of obviousness cannot be established.

This is not found persuasive because in a 103 obviousness rejection, a single reference does not need to teach or suggest every element of the independent claims, and if combination of prior arts teaches or suggests the claimed invention with proper motivation and expectation of success, the rejection is proper.

Applicants' furthermore argue that in Example 8, Vockley measured the arginase activity in solid tumor samples and normal adjacent tissues (col. 41, lines 211-39), one of skill in the art would understand that Vockley teaches away from administering either Arginase I or Arginase II polypeptides for the treatment of cancer.

The Examiner agrees that in Example 8, Vockley measured the arginase activity in solid tumor samples and normal adjacent tissues, wherein the activity is higher in solid tumor than adjacent tissues, however, one cannot ignore the fact that arginase II can be used for treating cancer as suggested by Vockley et al. Since, it is well known that arginase from liver, which is arginase I, is cytotoxic to cancer cells, that inhibits cancer cell growth or cytotoxic to cancer cells or even arginase modified with polyethylene glycol (PEG) can be used for treating cancer of mice in vivo, and one of ordinary skilled in the art would expect that arginase modified with PEG can be used for treating human cancer in vivo (see, evidential reference, abstract, page 261paragraph 1 and 2, Table 1, Savoca et al. 1984, see IDS).

In addition, Applicants' argue that Takaku teaches away from using arginase for the treatment of cancer because Takaku only showed that arginine deiminase exhibits anti-tumor activity and Takaku provided no evidence that other arginine degrading

enzymes could be used in place of arginine deiminase and explicitly stated that arginase would not be effective because it would not possess sufficient *in vivo* activity to produce anti-tumor effects.

This is not found persuasive because Takaku et al. do not need to teach or suggest using arginase, but one of ordinary skilled in the art would expect to test arginase from the teaching of Takaku et al. regarding anti-tumor activity of arginine deaminase in view of arginine degrading activity of arginase even though its activity is not sufficient in vivo, which means there are some activity that can be increased by modifying the arginase by PEG, which is well known in the art, and arginine deaminase.

Applicants also argue that according to Takaku, arginase "has not been applied to the treatment of human cancer because of its poor anti-tumor activity *in vivo,* and because Takaku teaches that not all arginine-degrading enzymes possess equivalent in vivo activity, one of skill in the art would not have a reason to modify or combine the references in the way alleged by the Office.

This is not found persuasive because Takaku et al. indeed teach anti-tumor activity of arginase in vivo, even though it is poor, which does not rule out that arginase does not have any anti-tumor activity in vivo and furthermore, Takaku et al. clearly teach that arginase inhibits cancer cell growth in vitro, which suggest that arginase may be degraded in vivo, which raised the possibility of using PEG-modified arginase, which is also well known in the prior art (see, Vockley et al. Col 14, paragraph 9, line 40-67) to have increased half-life (see, also evidential reference, Savoca et al., see IDS).

Therefore, Takaku et al. do not teaches away but suggest the use of arginase as anti-cancer agent even in vivo, although the effect is poor.

Therefore, the rejection is maintained.

Conclusion

Status of the claims:

Claims 47-56 are pending.

Claims 28 and 43-46 are rejected.

Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Iqbal Chowdhury, Patent Examiner

Art Unit 1652

/Richard G Hutson/
Primary Examiner, Art Unit 1652